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Amendments to the Claims:

This listing of claims replaces all prior versions and listings of claims in the application:

Listing of Claims:

1 to 207 (Canceled)

208. (New) An isolated protein having at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% amino acid identity compared to the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively, or an isolated fragment of such protein comprising at least 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 165, 170, 171, 172, 173, or 174 contiguous amino acids having said percentages of amino acid identity compared to the corresponding amino acids in SEQ ID NO:3 and SEQ ID NO:4, wherein said protein or fragment of such protein comprises an amino acid or an amino acid sequence which corresponds to

(a) a mutation in the mouse Agr2 protein as defined above which, if encoded by the mouse Agr2 gene and present in the genome of all or essentially all cells of a mouse in a homozygous manner, results in a phenotype associated with an alteration in goblet cell function compared to the corresponding wild-type animal; and/or

(b) a mutation in the mouse Agr2 protein or the human AGR2 protein as defined above which leads to an altered biological activity of the mutated protein when compared to the corresponding wild-type mouse Agr2 protein or human AGR2 protein in an in vitro assay selected from the group consisting of a colon cell proliferation assay, a goblet cell mucus secretion assay, and a *Xenopus laevis* cement gland differentiation assay; and/or

(c) a mutation of the human AGR2 protein as defined above which is indicative of an increased risk of a human subject of developing a medical condition associated with an alteration in goblet cell function, or indicative of an association of a medical condition in a human subject which is associated with an alteration in goblet cell function with altered AGR2 expression or function.

209. (New) The isolated protein or protein fragment according to claim 208, wherein said protein represents an orthologue of the mouse Agr2 or the human AGR2 protein, preferably a vertebrate orthologue, in particular an orthologue wherein said vertebrate is *Xenopus leavis*, or a mammalian orthologue, in particular an orthologue wherein said vertebrate is selected from the group consisting of a mouse, rat, rabbit, hamster, dog, cat, sheep, and horse.

210. (New) The isolated protein or protein fragment according to claim 208, wherein said alteration results in a loss of function phenotype.

211. (New) The isolated protein or protein fragment according to claim 208, wherein said alteration results in a gain of function phenotype.

212. (New) The isolated protein or protein fragment according to claim 208, wherein said alteration is an alteration in goblet cell differentiation, particularly terminal differentiation and/or goblet cell mucus production or secretion and/or mucus composition.

213. (New) The isolated protein or protein fragment according to claim 208, wherein said alteration is characterized by a reduction in pre-mucin storing granules in the goblet cells, an altered mucus secretion, secondary inflammatory infiltrations in the intestinal mucosal epithelium and submucosa.

214. (New) The isolated protein or protein fragment according to claim 208, wherein said phenotype is furthermore associated with an increased proliferation of the glandular epithelium of the Brunner's gland.

215. (New) The isolated protein or protein fragment according to claim 208, wherein said alteration results in diarrhea, or diarrhea and a thriving deficit.

216. (New) The isolated protein or protein fragment according to claim 208, wherein said medical condition is selected from the group consisting of asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, dry eye syndrome, gastric disease, peptic ulcer, inflammatory bowel disease, in particular Crohn's disease or ulcerative colitis, and intestinal cancer.

217. (New) The isolated protein or protein fragment according to claim 208, wherein said mutation results in a deletion or substitution by another amino acid of an amino acid of said mouse Agr2 protein or human AGR2 protein, or an insertion of additional amino acids not normally present in the amino acid sequence of said mouse Agr2 protein or said human AGR2 protein.

218. (New) The isolated protein or protein fragment according to claim 217, wherein the substitution of said amino acid of said mouse Agr2 protein or said human AGR2 protein by another amino acid is a non-conservative substitution.

219. (New) The isolated protein or protein fragment according to claim 217, wherein the amino acid of said mouse Agr2 protein or said human AGR2 protein that is deleted or substituted is Val 137.

220. (New) The isolated protein or protein fragment according to claim 219, wherein the substitution at position 137 is one of the following substitutions:

- a) Val → acidic amino acid such as Glu or Asp;
- b) Val → basic amino acid, such as His, Arg or Lys;
- c) Val → aliphatic hydroxyl side chain amino acid, such as Ser or Thr;
- d) Val → amide side chain amino acid, such as Asn or Gln;
- e) Val → sulfur containing side chain amino acid, such as Cys or Met;
- f) Val → aromatic side chain amino acid, such as Phe, Tyr, Trp;

- g) Val → Gly or Pro; and
- h) Val → Ala, Leu or Ile.

221. (New) The isolated protein or protein fragment according to claim 220, wherein the substitution at position 137 is a substitution of valine by glutamic acid.

222. (New) An isolated protein having the amino acid sequence set forth in SEQ ID NO:2 or SEQ ID NO:30, or an isolated fragment of such protein comprising at least 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 165, 170, 171, 172, 173, or 174 contiguous amino acids of said amino acid sequence, said contiguous amino acids comprising an amino acid corresponding to Glu 137.

223. (New) A fusion protein comprising a protein or protein fragment according to claim 208 fused to another protein or protein fragment not having said percentages of amino acid sequence identity to any corresponding amino acids in SEQ ID NO:3 and SEQ ID NO:4.

224. (New) The fusion protein of claim 223, wherein said other protein is a protein unrelated to the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively.

225. (New) An isolated nucleic acid encoding a protein or a fragment of such protein according to claim 208, or an isolated nucleic acid which is complementary thereto.

226. (New) An isolated nucleic acid having the nucleotide sequence set forth in SEQ ID NO:1 or SEQ ID NO:29, or an isolated nucleic acid which is complementary thereto.

227. (New) An episomal element comprising a nucleic acid as defined in claim 225.

228. (New) The episomal element according to claim 227, wherein said episomal element is selected from a plasmid, a cosmid, a bacterial phage nucleic acid, or a viral nucleic acid.

229. (New) A vector comprising a nucleic acid molecule encoding the protein according to claim 208.

230. (New) A host cell transfected with the episomal element of claim 227.

231. (New) A host cell transfected with the vector of claim 229.

232. (New) An antisense nucleic acid comprising a nucleotide sequence which is complementary to

(i) a part of an mRNA encoding a protein according to claim 208, said part encoding an amino acid sequence comprising the amino acid or amino acid sequence which corresponds to

(a) the mutation in the mouse Agr2 protein according to SEQ ID NO:3 which, if encoded by the mouse Agr2 gene and present in the genome of all or essentially all cells of a mouse in a homozygous manner, results in a phenotype associated with an alteration in goblet cell function compared to the corresponding wild-type animal, said phenotype optionally being furthermore associated with an increased proliferation of the glandular epithelium of the Brunner's gland; and/or

(b) the mutation in the mouse Agr2 protein or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively, which leads to an altered biological activity of the mutated protein when compared to the corresponding wild-type mouse Agr2 protein or human AGR2 protein in an in vitro assay selected from the group consisting of a colon cell proliferation assay, a goblet cell mucus secretion assay, and a *Xenopus laevis* cement gland differentiation assay; and/or

(c) the mutation of the human AGR2 protein according to SEQ ID NO:4 which is indicative of an increased risk of a human subject of developing a medical condition associated with an alteration in goblet cell function, or indicative of an association of a medical condition in a human subject which is associated with an alteration in goblet cell function with altered AGR2 expression or function;

(ii) a part of the mRNA encoding the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively, or an orthologue thereof having at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% amino acid identity compared to the mouse Agr2 or the human AGR2 protein as defined above, said part being a non-coding part and comprising a sequence corresponding to a mutation in the gene coding for said protein or orthologue which affects expression of said protein or orthologue; or

(iii) a part of the mRNA encoding a protein which affects expression or function of the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively, or an orthologue thereof having at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% amino acid identity compared to the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively.

233. (New) The antisense nucleic acid of claim 232, wherein said antisense nucleic acid is capable of hybridizing to said mRNA via said complementary nucleotide sequence under physiological conditions, or under conditions of high stringency, preferably under hybridization conditions of a high salt buffer comprising 6x SSC, 50 mM Tris-HCl (pH 7.5), 1 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.02% BSA, and 500 mg/ml denatured salmon sperm DNA at 65°C, followed by one or more washes in 0.2x SSC, 0.01% BSA at 50°C, furthermore preferably under hybridization conditions of a high salt buffer comprising 6x SSC, 50 mM Tris-HCl (pH 7.5), 1 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.02% BSA, and 500 mg/ml denatured salmon sperm DNA at 65°C, followed by one or more washes in 0.2x SSC, 0.01% BSA at 65°C.

234. (New) The antisense nucleic acid of claim 233, wherein said hybridization to said mRNA is more effective than hybridization to

(i) the mRNA encoding the same protein which, however, corresponds to the wild-type mouse Agr2 or human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4 in respect of said amino acid sequence;

(ii) the mRNA encoded by the wild-type gene of the mouse Agr2 or human AGR2 protein as defined above, or the wild-type gene of the corresponding orthologue; or

(iii) the mRNA encoded by the wild-type gene of the corresponding protein which affects expression or function of the mouse Agr2 or the human AGR2 protein as defined above.

235. (New) A host cell transformed with an antisense nucleic acid according to claim 232.

236. (New) The host cell according to claim 235, wherein said host cell is a eukaryotic cell.

237. (New) The host cell according to claim 235, wherein said host cell is a prokaryotic cell.

238. (New) A short interfering RNA (siRNA) comprising a double stranded nucleotide sequence wherein one strand is complementary to an at least 19, 20, 21, 22, 23, 24, or 25 nucleotide long segment of an mRNA encoding

(a) the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively, or an orthologue thereof having at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% amino acid identity compared to the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively; or

(b) a protein which affects expression or function of the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively, or an orthologue

thereof having at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% amino acid identity compared to the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively.

239. (New) The siRNA of claim 238, wherein said siRNA is capable of silencing or suppressing the expression of the AGR2 gene encoding said mRNA.

240. (New) The siRNA of claim 238, wherein said AGR2 gene is an AGR2 gene of a human subject unaffected by or known not to be at risk of developing a condition associated with an alteration in goblet cell function.

241. (New) The siRNA according to claim 238, wherein said segment includes sequences from the 5' untranslated (UT) region, the open reading frame (ORF), or the 3' UT region of said mRNA.

242. (New) A host cell transformed with an siRNA according to claim 238.

243. (New) The host cell according to claim 242, wherein said host cell is a eukaryotic cell.

244. (New) The host cell according to claim 242, wherein said host cell is a prokaryotic cell.

245. (New) An anticalin specifically binding an epitope in a protein which corresponds to

(a) the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively, or an orthologue thereof having at least 65%, 70%, 75%, 80%, 85%,

90%, 95%, 98%, or 99% amino acid identity compared to the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively; or

(b) a protein which affects expression or function of the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively, or an orthologue thereof having at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% amino acid identity compared to the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively.

246. (New) An aptamer specifically binding an epitope in a protein which corresponds to

(a) the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively, or an orthologue thereof having at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% amino acid identity compared to the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively; or

(b) a protein which affects expression or function of the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively, or an orthologue thereof having at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% amino acid identity compared to the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively.

247. (New) A non-human vertebrate animal comprising in the genome of at least some of its cells an allele of a gene encoding a protein having at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% amino acid identity compared to the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively, said allele comprising a mutation which,

a) if present in the genome of all or essentially all cells of said animal in a homozygous manner, results in a phenotype associated with an alteration in goblet cell function compared to the corresponding wild-type animal; and/or

b) corresponds to a mutation in the mouse Agr2 protein or the human AGR2 protein as defined above which leads to an altered biological activity of the mutated protein when compared to the corresponding wild-type mouse Agr2 protein or human AGR2 protein in an in vitro assay selected from the group consisting of a colon cell proliferation assay, a goblet cell mucus secretion assay, and a *Xenopus laevis* cement gland differentiation assay; and/or

c) corresponds to a mutation of the human AGR2 protein as defined above which is indicative of an increased risk of a human subject of developing a medical condition associated with an alteration in goblet cell function, or indicative of an association of a medical condition in a human subject which is associated with an alteration in goblet cell function with altered AGR2 expression or function.

248. (New) A non-human vertebrate animal comprising in the genome of at least some of its cells an allele of a gene coding for a protein which affects expression or function of the AGR2 protein of said animal, said allele comprising a mutation which, if present in the genome of all or essentially all cells of said animal in a homozygous manner, results in a phenotype associated with an alteration in goblet cell function compared to the corresponding wild-type animal.

249. (New) The animal according to claim 247, wherein said alteration results in a loss of function phenotype.

250. (New) The animal according to claim 247, wherein said alteration results in a gain of function phenotype.

251. (New) The animal according to claim 247, wherein said alteration is an alteration in goblet cell differentiation, particularly terminal differentiation, and/or goblet cell mucus production or secretion and/or mucus composition.

252. (New) The animal according to claim 247, wherein said alteration is characterized by a reduction in pre-mucin storing granules in the goblet cells, an altered mucus secretion, and secondary inflammatory infiltrations in the intestinal mucosal epithelium and submucosa.

253. (New) The animal according to claim 247, wherein said phenotype is furthermore associated with an increased proliferation of the glandular epithelium of the Brunner's gland.

254. (New) The animal according to claim 247, wherein said alteration results in diarrhea, or diarrhea and a thriving deficit.

255. (New) The animal according to claim 247, wherein said gene encodes a protein which is an orthologue of SEQ ID NO:3 and SEQ ID NO:4 with respect to said animal.

256. (New) The animal according to claim 247, wherein said gene encodes a protein according to claim 208.

257. (New) The animal according to claim 247, wherein said gene encodes a protein having the amino acid sequence of SEQ ID NO:2 or SEQ ID NO:30.

258. (New) The animal according to claim 247, wherein said animal is a transgenic animal.

259. (New) The animal according to claim 247, wherein said cells are the germ cells of said animal.

260. (New) The animal according to claim 247, wherein said cells are the somatic cells of said animal.

261. (New) The animal according to claim 247, wherein said genome of said cells is homozygous in respect of said allele.

262. (New) The animal according to claim 247, wherein said animal is a mammalian animal, preferably a rodent.

263. (New) The animal according to claim 262, wherein said animal is selected from the group consisting of a mouse, rat, rabbit, hamster, dog, cat, sheep, and horse.

264. (New) A method for the identification of a protein or nucleic acid diagnostic marker for a goblet cell-related disorder, or as an animal model for studying the molecular mechanisms of, or physiological processes associated with, a goblet cell-related disorder, or for the identification and testing of an agent useful in the prevention, amelioration, or treatment of a goblet cell-related disorder comprising administering said agent to the non-human vertebrate animal of claim 247 and measuring or monitoring a phenotypic parameter in said animal.

265. (New) The method according to claim 264, wherein said goblet cell-related disorder is selected from the group consisting of asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, dry eye syndrome, gastric disease, peptic ulcer, inflammatory bowel disease, in particular Crohn's disease or ulcerative colitis, and intestinal cancer.

266. (New) A method for studying the molecular mechanisms of, or physiological processes associated with, conditions associated with, or affected by, reduced activity or undesirable, e.g. increased, activity of endogenous AGR2; reduced expression, reduced production or undesirable, e.g. increased, production of endogenous AGR2; or for the identification and testing of an agent useful in the prevention, amelioration, or treatment of these

conditions comprising administering said agent to the non-human vertebrate animal of claim 247 and measuring or monitoring a phenotypic parameter in said animal.

267. (New) The method according to claim 264, wherein said agent is selected from the group consisting of a small molecule drug, a (poly)peptide, and a nucleic acid.

268. (New) The method according to claim 266, wherein said agent is selected from the group consisting of a small molecule drug, a (poly)peptide, and a nucleic acid.

269. (New) The agent of claim 267, wherein said agent is an antagonist of AGR2.

270. (New) The agent of claim 268, wherein said agent is an antagonist of AGR2.

271. (New) The agent of claim 267, wherein said agent is an agonist of AGR2.

272. (New) The agent of claim 268, wherein said agent is an agonist of AGR2.

273. (New) A method for studying or identifying protein or nucleic acid diagnostic markers, such as an early gene diagnostic marker, for diseases associated with AGR2 deficiency or over-expression comprising subjecting an organ or tissue of the non-human vertebrate animal according to claim 247 to procedures of proteomics or gene expression analysis.

274. (New) A method of identifying

(a) a protein or nucleic acid marker indicative of an increased risk of a human subject of developing a medical condition associated with an alteration in goblet cell function; or

(b) a protein or nucleic acid marker indicative of an association of a medical condition in a human subject which is associated with an alteration in goblet cell function with altered AGR2 expression or function

said method comprising the step of analyzing a test sample derived from a human subject for the presence of a difference compared to a similar test sample if derived from a human subject unaffected by or known not to be at risk of developing said condition, wherein said difference is indicative of the presence of a mutation in an allele of the gene coding for the AGR2 protein according to SEQ ID NO:4, or in an allele of a gene coding for a protein which affects expression or function of said AGR2 protein.

275. (New) The method of claim 274, wherein said test sample is analyzed for a difference compared to similar test samples if derived from a group of human subjects unaffected by, or known not to be at risk of developing, said condition.

276. (New) The method according to claim 274, wherein said human subject whose test sample is analyzed has a condition or is known or suspected to be at risk of developing a condition associated with an alteration in goblet cell function.

277. (New) The method of claim 274, further comprising the step of obtaining said similar test sample from said human subject unaffected by, or known not to be at risk of developing, said condition.

278. (New) The method according to claim 274, wherein said alteration is an alteration in goblet cell differentiation, particularly terminal differentiation, and/or goblet cell mucus production or secretion and/or mucus composition.

279. (New) The method according to claim 274, wherein said alteration is characterized by a reduction in pre-mucin storing granules in the goblet cells, an altered mucus secretion, and secondary inflammatory infiltrations in the intestinal mucosal epithelium and submucosa.

280. (New) The method according to claim 274, wherein said medical condition is furthermore associated with an increased proliferation of the glandular epithelium of the Brunner's gland.

281. (New) The method according to claim 274, wherein said alteration results in diarrhea.

282. (New) The method according to claim 274, wherein said medical condition is selected from the group consisting of asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, dry eye syndrome, gastric disease, peptic ulcer, inflammatory bowel disease, in particular Crohn's disease or ulcerative colitis, and intestinal cancer.

283. (New) The method according to claim 274, wherein said medical condition is associated with an increase in mucus production.

284. (New) The method according to claim 274, wherein said test sample is a nucleic acid sample.

285. (New) The method according to claim 284, wherein the step of analyzing said nucleic acid sample comprises amplifying at least a portion of its nucleic acid via the polymerase chain reaction, and optionally also amplifying via the polymerase chain reaction at least a portion of the nucleic acid of said similar sample or said similar samples.

286. (New) The method according to claim 274, wherein said test sample is a protein sample.

287. (New) The method according to claim 286, wherein said protein is the AGR2 protein.

288. (New) The method according to claim 274, wherein said mutation results in a deletion or substitution by another amino acid of an amino acid of the AGR2 protein encoded by said allele, or an insertion of additional amino acids not normally present in the amino acid sequence of the AGR2 protein according to SEQ ID NO:4.

289. (New) The method according to claim 288, wherein the substitution of said amino acid of the AGR2 protein by another amino acid is a non-conservative substitution.

290. (New) The method according to claim 288, wherein said amino acid of the AGR2 protein that is deleted or substituted is Val 137.

291. (New) The method according to claim 290, wherein the substitution at position 137 is one of the following substitutions:

- a) Val → acidic amino acid such as Glu or Asp;
- b) Val → basic amino acid, such as His, Arg or Lys;
- c) Val → aliphatic hydroxyl side chain amino acid, such as Ser or Thr;
- d) Val → amide side chain amino acid, such as Asn or Gln;
- e) Val → sulfur containing side chain amino acid, such as Cys or Met;
- f) Val → aromatic side chain amino acid, such as Phe, Tyr, Trp;
- g) Val → Gly or Pro; and
- h) Val → Ala, Leu or Ile.

292. (New) The method according to claim 291, wherein the substitution at position 137 is a substitution of valine by glutamic acid.

293. (New) A method for identifying a predisposition of a human subject for developing a medical condition associated with an alteration in goblet cell function, said method

comprising the step of determining whether a test sample derived from said human subject indicates the presence of a mutation in an allele of the gene coding for the AGR2 protein according to SEQ ID NO:4 indicative of an increased risk of said human subject of developing said medical condition.

294. (New) The method according to claim 293, further comprising the step of assigning a certain risk of developing said medical condition to said human subject.

295. (New) A method for determining whether a medical condition in a human subject which is associated with an alteration in goblet cell function is associated with altered AGR2 expression or function, said method comprising the step of determining whether a test sample derived from said human subject indicates the presence of a mutation in an allele of the gene coding for the AGR2 protein according to SEQ ID NO:4 indicative of an altered AGR2 expression or function.

296. (New) The method according to claim 295, further comprising the step of assigning an association with altered AGR2 expression or function to said human subject's medical condition.

297. (New) The method according to claim 293, wherein said alteration is an alteration in goblet cell differentiation, particularly terminal differentiation, and/or goblet cell mucus production or secretion and/or mucus composition.

298. (New) The method according to claim 295, wherein said alteration is an alteration in goblet cell differentiation, particularly terminal differentiation, and/or goblet cell mucus production or secretion and/or mucus composition.

299. (New) The method according to claim 293, wherein said alteration is characterized by a reduction in pre-mucin storing granules in the goblet cells, an altered mucus secretion, and secondary inflammatory infiltrations in the intestinal mucosal epithelium and submucosa.

300. (New) The method according to claim 295, wherein said alteration is characterized by a reduction in pre-mucin storing granules in the goblet cells, an altered mucus secretion, and secondary inflammatory infiltrations in the intestinal mucosal epithelium and submucosa.

301. (New) The method according to claim 293, wherein said medical condition is selected from the group consisting of asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, dry eye syndrome, gastric disease, peptic ulcer, inflammatory bowel disease, in particular Crohn's disease or ulcerative colitis, and intestinal cancer.

302. (New) The method according to claim 293, wherein said medical condition is associated with an increase in mucus production.

303. (New) The method according to claim 295, wherein said medical condition is selected from the group consisting of asthma, chronic obstructive pulmonary disease (COPD), cystic fibrosis, dry eye syndrome, gastric disease, peptic ulcer, inflammatory bowel disease, in particular Crohn's disease or ulcerative colitis, and intestinal cancer.

304. (New) The method according to claim 295, wherein said medical condition is associated with an increase in mucus production.

305. (New) The method according to claim 293, wherein said test sample is a nucleic acid sample.

306. (New) The method according to claim 295, wherein said test sample is a nucleic acid sample.

307. (New) The method according to claim 293, wherein said test sample is a protein sample.

308. (New) The method according to claim 295, wherein said test sample is a protein sample.

309. (New) The method according to claim 307, wherein said protein is the AGR2 protein.

310. (New) The method according to claim 308, wherein said protein is the AGR2 protein.

311. (New) The method according to claim 293, wherein said mutation results in a deletion or substitution by another amino acid of an amino acid of the AGR2 protein encoded by said allele, or an insertion of additional amino acids not normally present in the amino acid sequence of the AGR2 protein according to SEQ ID NO:4.

312. (New) The method according to claim 295, wherein said mutation results in a deletion or substitution by another amino acid of an amino acid of the AGR2 protein encoded by said allele, or an insertion of additional amino acids not normally present in the amino acid sequence of the AGR2 protein according to SEQ ID NO:4.

313. (New) The method according to claim 311, wherein said amino acid of the AGR2 protein that is deleted or substituted is Val 137.

314. (New) The method according to claim 312, wherein said amino acid of the AGR2 protein that is deleted or substituted is Val 137.

315. (New) The method according to claim 313, wherein the substitution at position 137 is one of the following substitutions:

- a) Val → acidic amino acid such as Glu or Asp;
- b) Val → basic amino acid, such as His, Arg or Lys;
- c) Val → aliphatic hydroxyl side chain amino acid, such as Ser or Thr;
- d) Val → amide side chain amino acid, such as Asn or Gln;
- e) Val → sulfur containing side chain amino acid, such as Cys or Met;
- f) Val → aromatic side chain amino acid, such as Phe, Tyr, Trp;
- g) Val → Gly or Pro; and
- h) Val → Ala, Leu or Ile.

316. (New) The method according to claim 314, wherein the substitution at position 137 is one of the following substitutions:

- i) Val → acidic amino acid such as Glu or Asp;
- j) Val → basic amino acid, such as His, Arg or Lys;
- k) Val → aliphatic hydroxyl side chain amino acid, such as Ser or Thr;
- l) Val → amide side chain amino acid, such as Asn or Gln;
- m) Val → sulfur containing side chain amino acid, such as Cys or Met;
- n) Val → aromatic side chain amino acid, such as Phe, Tyr, Trp;
- o) Val → Gly or Pro; and
- p) Val → Ala, Leu or Ile.

317. (New) The method according to claim 315, wherein the substitution at position 137 is a substitution of valine by glutamic acid.

318. (New) The method according to claim 316, wherein the substitution at position 137 is a substitution of valine by glutamic acid.

319. (New) The method according to claim 293, wherein said gene codes for a AGR2 protein having the sequence set forth in SEQ ID NO:30.

320. (New) The method according to claim 295, wherein said gene codes for a AGR2 protein having the sequence set forth in SEQ ID NO:30.

321. (New) A pharmaceutical composition comprising an antisense nucleic acid according to claim 232 and a pharmaceutically acceptable carrier.

322. (New) A pharmaceutical composition comprising an siRNA according to claim 238 and a pharmaceutically acceptable carrier.

323. (New) A pharmaceutical composition comprising an anticalin according to claim 245 and a pharmaceutically acceptable carrier.

324. (New) A pharmaceutical composition comprising an aptamer according to claim 246 and a pharmaceutically acceptable carrier.

325. (New) A method of producing a mutant AGR2 protein comprising culturing a host cell according to claim 230 in a suitable medium under conditions such that the protein is expressed, and harvesting the cells or the medium.

326. (New) The method according to claim 325, wherein the protein is subsequently further purified from said cells or said medium.

327. (New) A method of gene therapy comprising delivering to cells in a human subject suffering from or known to be at risk of developing a condition associated with an alteration in goblet cell function a DNA construct comprising

(a) a sequence of an allele of the AGR2 gene encoding the human AGR2 protein according to SEQ ID NO:4, or encoding a protein having at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% amino acid identity compared to the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively; or a sequence of an allele of the AGR2 gene of a human subject unaffected by or known not to be at risk of developing said condition;

(b) a DNA sequence encoding the human AGR2 protein according to SEQ ID NO:4, or a human AGR2 protein encoded by the AGR2 gene of a human subject unaffected by or known not to be at risk of developing said condition, or a protein having at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% amino acid identity compared to the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively; or

(c) a DNA sequence encoding an antisense nucleic acid according to claim 232, or an antisense nucleic acid comprising a nucleotide sequence which is complementary to an mRNA encoded by the AGR2 gene of a human subject unaffected by or known not to be at risk of developing said condition.

328. (New) A method of gene therapy comprising delivering to cells in a human subject suffering from or known to be at risk of developing a condition associated with an alteration in goblet cell function a DNA construct comprising a DNA sequence encoding an siRNA according to claim 238.

329. (New) A method of gene therapy comprising delivering to cells in a human subject suffering from or known to be at risk of developing a condition associated with an alteration in goblet cell function a DNA construct comprising a DNA sequence encoding an aptamer according claim 246.

330. (New) The method of claim 327, wherein said human AGR2 gene of a subject unaffected by or known not to be at risk of developing said condition is a gene encoding a human AGR2 protein according to SEQ ID NO:4.

331. (New) The method of claim 327, wherein said cells are intestinal cells of said human subject, preferably goblet cells.

332. (New) The method of claim 328, wherein said cells are intestinal cells of said human subject, preferably goblet cells.

333. (New) The method of claim 329, wherein said cells are intestinal cells of said human subject, preferably goblet cells.

334. (New) The method of claim 327, wherein said cells are gastrointestinal cells of said human subject, preferably goblet cells and/or mucus secreting cells of the Brunner's gland.

335. (New) The method of claim 328, wherein said cells are gastrointestinal cells of said human subject, preferably goblet cells and/or mucus secreting cells of the Brunner's gland.

336. (New) The method of claim 329, wherein said cells are gastrointestinal cells of said human subject, preferably goblet cells and/or mucus secreting cells of the Brunner's gland.

337. (New) The method of claim 327, wherein the DNA construct is a viral vector.

338. (New) The method of claim 328, wherein the DNA construct is a viral vector.

339. (New) The method of claim 329, wherein the DNA construct is a viral vector.

340. (New) The method of claim 327, wherein said DNA construct is capable of directing expression of said protein, said antisense nucleic acid, or said siRNA.

341. (New) The method of claim 328, wherein said DNA construct is capable of directing expression of said protein, said antisense nucleic acid, or said siRNA.

342. (New) The method of claim 329, wherein said DNA construct is capable of directing expression of said protein, said antisense nucleic acid, or said siRNA.

343. (New) The method of claim 327, wherein said sequence of an allele of the AGR2 gene comprises coding sequences of said gene.

344. (New) The method of claim 328, wherein said sequence of an allele of the AGR2 gene comprises coding sequences of said gene.

345. (New) The method of claim 329, wherein said sequence of an allele of the AGR2 gene comprises coding sequences of said gene.

346. (New) A method of preventing, treating, or ameliorating a medical condition in a human subject associated with an alteration in goblet cell function, said method comprising administering to said human subject a pharmaceutical composition comprising an agent capable of modulating AGR2 activity in said human subject.

347. (New) The method according to claim 346, wherein said medical condition is associated with an increase in mucus production.

348. (New) The method of claim 346, wherein said pharmaceutical composition is a pharmaceutical composition according to claim 321.

349. (New) The method of claim 346, wherein said pharmaceutical composition is a pharmaceutical composition according to claim 322.

350. (New) The method of claim 346, wherein said pharmaceutical composition is a pharmaceutical composition according to claim 323.

351. (New) The method of claim 346, wherein said pharmaceutical composition is a pharmaceutical composition according to claim 324.

352. (New) The method according to claim 346, wherein said agent capable of modulating AGR2 activity in said human subject is

(a) an isolated protein having the sequence of the human AGR2 protein according to SEQ ID NO:4,

(b) an isolated protein having at least 65%, 70%, 75%, 80%, 85%, 90%, 95%, 98%, or 99% amino acid identity compared to the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively, wherein said protein shows the same or essentially the same activity as the human AGR2 protein according to SEQ ID NO:4 in an in vitro assay selected from the group consisting of a colon cell proliferation assay, a goblet cell mucus secretion assay, and a *Xenopus laevis* cement gland differentiation assay;

(c) an isolated fragment of the protein according to (a) or (b) above comprising at least 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 165, 170, 171, 172, 173, or 174 contiguous amino acids having said percentages of amino acid identity compared to the corresponding amino acids in SEQ ID NO:3 and SEQ ID NO:4, wherein said fragment shows the same or essentially the same activity as the human AGR2 protein according to SEQ ID NO:4 in an in vitro assay selected from the group consisting of a

colon cell proliferation assay, a goblet cell mucus secretion assay, and a *Xenopus laevis* cement gland differentiation assay;

(d) a fusion protein comprising a protein or protein fragment according to (a) to (c) above fused to another protein or protein fragment not having said percentages of amino acid sequence identity to any corresponding amino acids in SEQ ID NO:3 and SEQ ID NO:4; preferably fused to a protein unrelated to the mouse Agr2 or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively;

(e) an antibody specifically recognizing an epitope comprised within the human AGR2 protein according to SEQ ID NO:4, or within a human AGR2 protein encoded by the AGR2 gene of a human subject unaffected by or known not to be at risk of developing a medical condition associated with altered goblet cell function; or

(f) an antisense nucleic acid comprising a nucleotide sequence which is complementary to an mRNA encoded by the AGR2 gene of a human subject unaffected by or known not to be at risk of developing said condition, preferably encoded by the AGR2 gene encoding the human AGR2 protein according to SEQ ID NO:4.

353. (New) A method of identifying an agent useful in the prevention, amelioration, or treatment of a goblet cell-related disorder, the method comprising

a) culturing mammalian goblet cells in the presence or absence of a candidate agent; and

b) determining whether the presence of the agent results in an increase in the production by the cells of mucus and/or one or more particular mucus constituents;

wherein said goblet cells show a reduced or no expression of the AGR2 protein, or carry a mutation in one or both alleles of their endogenous AGR2 gene so that the allele is no longer capable of being expressed, or that it encodes a protein according to claim 208.

354. (New) A method of identifying an agent useful in the prevention, amelioration, or treatment of a goblet cell-related disorder, the method comprising

a) culturing mammalian goblet cells in the presence or absence of a candidate agent;
and

b) determining whether the presence of the agent results in a decrease in the production by the cells of mucus and/or one or more particular mucus constituents;

wherein said goblet cells show an increased expression of the AGR2 protein, or carry a mutation in one or both alleles of their endogenous AGR2 gene so that the allele shows an increased amount of expression or that it encodes a protein according to claim 208.

355. (New) A method of identifying an antagonist of the AGR2 protein, the method comprising

a) culturing mammalian goblet cells in the presence or absence of a wild-type mammalian AGR2 protein, preferably the mouse Agr2 protein or the human AGR2 protein according to SEQ ID NO:3 and SEQ ID NO:4, respectively; and

b) determining whether a decrease in the production of mucus and/or one or more particular mucus constituents by the cells which are cultured in the presence of said wild-type AGR2 protein is observed upon the addition of a candidate antagonist agent to the cultured cells.

356. (New) The method according to claim 355, wherein said goblet cells show a reduced or no expression of the AGR2 protein, or carry a mutation in one or both alleles of their endogenous AGR2 gene so that the allele is no longer capable of being expressed or that it encodes a protein according to claim 208.

357. (New) The method according to claim 353, wherein said cells are homozygous for said mutated endogenous AGR2 allele.

358. (New) The method according to claim 354, wherein said cells are homozygous for said mutated endogenous AGR2 allele.

359. (New) The method according to claim 353, wherein said cells do not additionally contain a functional allele of a wild type AGR2 gene (i.e., no functional allele of the corresponding wild type orthologue, or of a heterologous wild type AGR2 gene), or a nucleic acid sequence expressing a wild type AGR2 protein (representing either the corresponding wild type orthologue, or a heterologous wild type AGR2 protein).

360. (New) The method according to claim 353, wherein the mucus constituent is mucin2 or a trefoil peptide.

361. (New) The method according to claim 354, wherein the mucus constituent is mucin2 or a trefoil peptide.

362. (New) The method according to claim 355, wherein the mucus constituent is mucin2 or a trefoil peptide.

363. (New) The method according to claim 353, wherein said mammalian goblet cells are LS174T or HT29 cells.

364. (New) The method according to claim 354, wherein said mammalian goblet cells are LS174T or HT29 cells.

365. (New) The method according to claim 355, wherein said mammalian goblet cells are LS174T or HT29 cells.

366. (New) The method according to claim 353, wherein the candidate agent is selected from the group consisting of

- a) a peptide or polypeptide;
- b) a nucleic acid (including a peptide nucleic acid); and

c) a small molecule having a molecular weight of no more than 2000 Dalton, preferably no more than 1500 Dalton, more preferably no more than 1000 Dalton, and most preferably no more than 500, 400, 300, or even 200 Dalton.

367. (New) The method according to claim 354, wherein the candidate agent is selected from the group consisting of

- a) a peptide or polypeptide;
- b) a nucleic acid (including a peptide nucleic acid); and
- c) a small molecule having a molecular weight of no more than 2000 Dalton, preferably no more than 1500 Dalton, more preferably no more than 1000 Dalton, and most preferably no more than 500, 400, 300, or even 200 Dalton.

368. (New) The method according to claim 355, wherein the candidate agent is selected from the group consisting of

- a) a peptide or polypeptide;
- b) a nucleic acid (including a peptide nucleic acid); and
- c) a small molecule having a molecular weight of no more than 2000 Dalton, preferably no more than 1500 Dalton, more preferably no more than 1000 Dalton, and most preferably no more than 500, 400, 300, or even 200 Dalton.

369. (New) An agent identified or identifiable by a method according claim 353.

370. (New) An agent identified or identifiable by a method according claim 354.

371. (New) An agent identified or identifiable by a method according claim 355.